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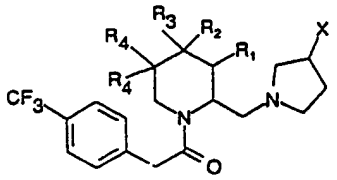


(I)

(57) Abstract

Azacyclic derivatives of formula (I), are kappa-receptor agonists and are useful in the treatment of convulsions, cough, asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states and cerebral ischaemia.

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# 2-(PYRROLIDINYL-1-METHYL)-PIPERIDINE DERIVATIVES AND THEIR USE AS KAPPA-RECEPTOR AGONISTS

This invention is concerned with novel substituted azacyclic derivatives, processes for their preparation, and their use in medicine, particularly, but not exclusively, as analgesics.

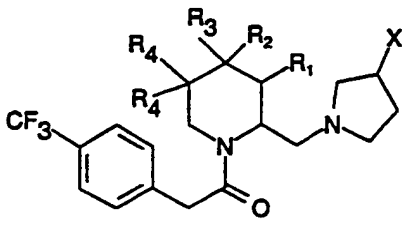
Compounds which are kappa-receptor agonists act as analgesics through interaction with kappa opioid receptors. The advantage of kappa-receptor agonists over the classical μ-receptor agonists, such as morphine, lies in their ability to cause analgesia while being devoid of morphine-like behavioural effects and addiction liability.

EP-A-330461, 330467 and 330469 (Glaxo Group Ltd), EP-A-361791 and WO 91/08206 (Dr Lo Zambeletti) disclose groups of azacyclic derivatives which are stated to exhibit kappa-receptor agonism, and which are said to be of potential therapeutic utility in the treatment of pain and cerebral ischaemia.

A small group of structurally related substituted azacyclic derivatives have now been discovered which also exhibit potent kappa-receptor agonism without some of the undesirable behavioural effects of morphine and morphine analogues, and are therefore of potential use in the treatment of pain.

The new derivatives are also of potential use in other therapeutic treatments which are associated with kappa agonists, in particular the treatment of convulsions, cough, asthma, inflammation (including inflammation pain), pancreatitis, arrhythmias, hyponatraemic disease states and cerebral ischaemia.

According to the present invention, there is provided a compound of formula (I), or a solvate or salt thereof,



(I)

in which each of $R_1$, $R_2$, $R_3$ and $R_4$ is hydrogen or methyl, and/or $R_1$, $R_2$ and $R_3$ together form a =CH-CH=CH-CH= group, and X is hydroxy or fluoro.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of a compound of formula (I) or its salt or solvate.

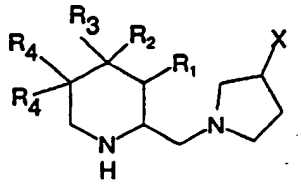
One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of a pharmaceutically acceptable salt of the compounds of formula (I) include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Examples of a pharmaceutically acceptable solvate of the compounds of formula (I) include hydrates.

The compounds of formula (I) have at least one asymmetric centre and therefore exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including racemates.

The present invention also provides a process for the preparation of a compound of formula (I) which comprises reacting 4-trifluoromethylphenylacetic acid, or an active derivative thereof, with a compound of formula I(a)



(Ia)

in which $R_1$, $R_2$, $R_3$, $R_4$ and X are as defined in formula (I), and then optionally forming a salt and/or solvate of the obtained compound of formula (I).

A suitable active derivative of 4-trifluoromethylphenyl-acetic acid is the acid chloride.

The compounds of formula (I) may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example hydrates may be formed by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

As mentioned earlier, the compounds of formula (I) exist in more than one stereoisomeric form and the processes of the invention produce mixtures thereof. The individual isomers may be separated one from another by resolution using an optically active acid such as tartaric acid. Alternatively, an asymmetric synthesis may be used.

Compounds of formula (I(a)) may be prepared from known compounds by known methods, such as those described in WO 91/08206.

For example, the (R,S;R,S) compound of formula I(a) in which X is hydroxy, $R_1$ is hydrogen, $R_2$ and $R_3$ are both methyl, and $R_4$ is hydrogen, may be prepared according to the method described in Descriptions 1(a) and 1(b) of WO 91/08206, but starting from N-ethoxycarbonyl-4,4-dimethyl pipecolic acid instead of 1-ethoxycarbonylpipecolic acid. In this method, N-ethoxycarbonyl-4,4-dimethylpipecolic acid is treated firstly with thionylchloride in dry methylene chloride, and

the reaction mixture is then treated with 3-hydroxypyrrolidine to produce 2-(3-hydroxypyrrolidin-1-yl) carbonyl piperidine. Reduction of this with $LiAlH_4$ in an inert nitrogen atmosphere, yields the desired compound.

The (S,S) compound of formula (I) in which X is fluorine, and $R_1$, $R_2$, $R_3$ and $R_4$ are hydrogen, may be prepared according to the method described in Descriptions 1(a) and 1(c) of WO 91/08206, starting from enantiomerically pure reagents. In this method, 2-(3-fluoropyrrolidin-1-yl)carbonyl piperidine in dry THF is treated with borane dimethylsulphide complex in an inert nitrogen atmosphere.

The activity of the compounds of formula (I) in standard tests indicates that they are of potential therapeutic utility in the treatment of pain, hyponatraemic disease states, cerebral ischaemia, convulsions, cough, asthma, inflammation (including inflammation pain), arrhythmias, and pancreatitis (hereinafter referred to as the 'Conditions').

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Conditions.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of known compositions for treating the Conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the Conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, inhalation, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges,

reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl- pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid

compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable

carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned earlier, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention, when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

Compounds of this invention and their preparation are illustrated in the following Examples, the Descriptions illustrating the preparation of intermediates.

The compounds of the Examples are summarised in Table 1, and the pharmacological data are summarised in Table II.

Description 1

2-[(3S)-3-fluoropyrrolidin-1-yl]carbonyl-4,4-dimethyl piperidine - stereoisomer A -

12.95 ml (0.177 moles) of redistilled thionyl chloride were added dropwise under stirring to a solution fo 6.35 g (0.028 moles) of (R,S)-N-ethoxycarbonyl-4,4-dimethyl pipecolic acid dissolved in 90 ml of dry methylene chloride and kept below -10°C.
The reaction mixture was allowed to reach room temperature and left overnight.
The solvent was evaporated in vacuo to dryness and the residue, dissolved in 15 ml of dry methylene chloride, was added dropwise to a solution of 5.75 g (0.046 moles) of (3S)-3-fluoropyrrolidine hydrochloride [ WO 91 / 08206 ] dissolved in 60 ml of dry methylene chloride and kept below 0°C.
The reaction mixture was allowed to reach room temperature and left overnight.
100 ml of methylene chloride were added and the organic solution washed twice with 25% $K_2CO_3$ (30 ml).
Evaporation of the solvent in vacuo afforded the crude mixture of enantiomerically pure diastereoisomers.
The less polar product, stereoisomer A, was obtained by silica gel flash column chromatography, eluting with a mixture of $CH_2Cl_2$ /MeOH/28% $NH_4OH$, 94.5:5:0.5 respectively and was recrystallized from $(i\text{-}Pr)_2O$ to yield 820 mg of the title compound as a white powder.

$C_{12}H_{21}FN_2O$

M.P. = 97-98°C
M.W. = 228.304

$[\alpha]_D^{20}$ = -31.9 (C=1, MeOH)

Description 2

2-[(3S)-3-fluoropyrrolidin-1-yl]methyl-4,4-dimethyl piperidine - stereoisomer A -

The compound was prepared according to the method described in Description 1c of WO 91 / 08206 , starting from 820 mg (3.6 mmoles) of the compound of Description 1 of the present invention.
700 mg of the title compound were obtained and used in the subsequent reaction without further purification.

$C_{12}H_{23}FN_2$

M.W. = 214.320

Description 3

(R,S)-1-[(3S)-3-fluoropyrrolidin-1-yl]methyl-1,2,3,4-tetrahydroisoquinoline - mixture of diastereoisomers.

The compound was prepared following Description 2 of WO 91 / 08206 and starting from 4 g (18.51 mmoles) of 1-chloromethyl-3,4-dihydroisoquinoline hydrochloride [J. Am. Chem. Soc. 59, 2555 (1933)] and 4.9 g (39.65 mmoles) of (3S)-3-fluoropyrrolidine hydrochloride.
3.37 g of the title compound were obtained and used in the subsequent reaction without further purification.

$C_{14}H_{19}FN_2$

M.W. = 234.308

Description 4

(R,S)-1-[(3S)-3-fluoropyrrolidin-1-yl]methyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-mixture of diastereoisomers.

The compound was prepared following Description 2 of WO 91 / 08206 and starting from 4 g (16.38 mmoles) of 1-chloromethyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride [EP-A-409489] and 4.6 g (37.22 mmoles) of (3S)-3-fluoropyrrolidine hydrochloride.
2.84 g of the title compound were obtained and used in the subsequent reaction without further purification.

$C_{16}H_{23}FN_2$

M.W. = 262.360

Description 5

(R,S)-2-[(3S)-3-hydroxypyrrolidin-1-yl]methyl-4,4-dimethylpiperidine - mixture of diastereoisomers.

The compound was prepared following Descriptions 1a and 1b of WO 91 / 08206 and starting from 2.75 g (12.00 mmoles) of (RS)-N-ethoxycarbonyl-4,4-dimethyl pipecolic acid and 2.61 g (29.95 mmoles) of (3S)-3-hydroxypyrrolidine.
2.0 g of title compound were obtained and used in the subsequent reaction without further purification.

$C_{12}H_{24}N_2O$

M.W. = 212.328

Example 1

1-(4-trifluoromethylphenyl)acetyl-2-(3-hydroxypyrrolidin-1-yl) methyl-4,4-dimethyl piperidine hydrochloride. Diastereoisomeric mixture.

1.50 g (6.71 mmoles) of distilled 4-trifluoromethylphenyl acetyl chloride, dissolved in 10 ml of dry chloroform, were added dropwise at -20°C to a stirred solution of 1.20 g (5.65 mmoles) of 2-(3-hydroxypyrrolidin-1-yl)methyl-4,4-dimethyl piperidine - diast. mix. - dissolved in 35 ml of dry chloroform. The reaction mixture was allowed to reach room temperature and stirred overnight.
The organic solution was treated with 10% $K_2CO_3$, washed with water and dried over $Na_2SO_4$; the solvent was evaporated in vacuo to dryness and the residue purified by 230-400 mesh silica gel flash column chromatography, eluting with a mixture of $CH_2Cl_2$/ MeOH/28% $NH_4OH$, 95:5:0.5 respectively.
The so obtained pure free base was dissolved in 25 ml of ethyl acetate and the solution brought to acidic pH with $HCl/Et_2O$. The precipitate was filtered, washed and dried, to yield 700 mg of the title compound.

$C_{21}H_{29}F_3N_2O_2.HCl$

M.P. = 178-180°C
M.W. = 434.923

Elemental analysis: Calcd. C, 57.99; H, 6.95; N, 6.44;
Cl, 8.15; F, 13.11;
Found C, 58.04; H, 6.98; N, 6.43;
Cl, 8.27; F, 13.02.

I.R. (KBr) : 3270, 2960, 1625, 1330, 1120 $cm^{-1}$

Example 2

(2S)-1-(4-trifluoromethylphenyl)acetyl-2-[(3S)-3-fluoropyrrolidin-1-yl]methyl piperidine hydrochloride hemihydrate.

1.58 g (7.06 mmoles) of distilled 4-trifluoromethylphenyl acetyl chloride, dissolved in 10 ml of dry chloroform, were added dropwise at -10°C to a stirred solution of 1.20 g (6.45 mmoles) of (2S)-[(3S)-3-fluoropyrrolidin-1-yl]methyl piperidine dissolved in 35 ml of dry chloroform in the presence of 1.00 g (7.24 mmoles) of anhydrous potassium carbonate. The reaction mixture was allowed to reach room temperature and stirred overnight, washed with water , 5% $NaHCO_3$ and the organic solution dried over $Na_2SO_4$; the solvent was evaporated in vacuo to dryness and the residue purified by 230-400 mesh silica gel flash column chromatography, eluting with ethyl acetate containing 0.6% of 28% $NH_4OH$.
The so obtained pure free base was dissolved in 30 ml of ethyl acetate and the solution brought to acidic pH with $HCl/Et_2O$. The precipitate was filtered, washed and dried, to yield 1.3 g of the title compound.

$C_{19}H_{24}F_4N_2O$ .HCl .1/2 $H_2O$

M.P. = 151-153°C
M.W. = 417.871

$[\alpha]_D^{20}$ = -45.3 (C=1, MeOH)

Elemental analysis: Calcd. C, 54.61; H, 6.27; N, 6.70;
Cl, 8.49; F, 18.19;
Found C, 54.62; H, 6.22; N, 6.66;
Cl, 8.53; F, 18.32.

I.R. (KBr) : 3340, 2940, 1635, 1330, 1120, 1065 $cm^{-1}$

Example 3

1-(4-trifluoromethylphenyl)acetyl-2-[(3S)-3-fluoropyrrolidin-1-yl] methyl-4,4-dimethyl piperidine hydrochloride - stereoisomer A -

Prepared as described in Example 2, starting from 700 mg (3.27 mmoles) of 2-[(3S)-3-fluoropyrrolidin-1-yl] methyl-4,4-dimethyl piperidine - stereoisomer A -, 940 mg (4.22 mmoles) of distilled 4-trifluoromethylphenyl acetyl chloride and 450 mg (3.27 mmoles) of anhydrous potassium carbonate in 20 ml of dry methylene chloride.
The crude product was purified by silica gel flash column chromatography, eluting with a mixture of EtOAc/n-hexane/28% $NH_4OH$, 40:10:0.3 respectively to yield 800 mg of the pure free base which was dissolved in EtOAc and the solution brought to acidic pH with $HCl/Et_2O$.
The precipitate was filtered, washed and dried to yield 700 mg of the title compound.

$C_{21}H_{28}F_4N_2O \cdot HCl$

M.P. = 156-157°C
M.W. = 436.915

$[\alpha]_D^{20} = -33.8$ (C = 1, MeOH)

Elemental analysis: Calcd. C, 57.73; H, 6.69; N, 6.41; Cl, 8.12; F, 17.39;
Found C, 57.75; H, 6.72; N, 6.38; Cl, 8.18; F, 17.27.

I.R. (KBr) : 3450; 2960; 2930; 1625; 1615; 1425; 1330; 1160; 1110; 1065 $cm^{-1}$

On the basis of the sign of the optical rotation and of its pharmacological activity, in analogy with other structurally related compounds [Chirality, (1992), 4 (1), 8-15] , the (S) configuration at the unspecified chiral center may be assigned to the above mentioned enantiomerically pure stereoisomer A.

Example 4

(R,S)-1-[(3S)-3-fluropyrrolidin-1-yl]methyl-2-(4-trifluoromethyl phenyl)acetyl-1,2,3,4-tetrahydroisoquinoline hydrochloride.

Prepared as described in Example 2, starting from 1.43 g (6.10 mmoles) of (R,S)-1-[(3S)-3-fluoropyrrolidin-1-yl]methyl-1,2,3,4-tetrahydroisoquinoline, 1.7 g (7.63 mmoles) of distilled 4-trifluoromethylphenyl acetyl chloride and 0.8 g (5.80 mmoles) of anhydrous potassium carbonate in 25 ml of dry methylene chloride. The crude product was purified by silica gel flash column chromatography, eluting with a mixture of EtOAc/n-hexane/28% $NH_4OH$, 40:10:0.2 respectively to yield 1.8 g of the pure free base which was dissolved in ethyl acetate and the solution brought to acidic pH with $HCl/Et_2O$.
The precipitate was filtered, washed and dried to yield 1.6 g of the title compound.

$C_{23}H_{24}F_4N_2O \cdot HCl$

M.P. = 195-197°C
M.W. = 456.903

Elemental analysis: Calcd. C, 60.45; H, 5.51; N, 6.13;
Cl, 7.76; F, 16.63;
Found C, 60.22; H, 5.48; N, 6.08;
Cl, 7.63; F, 16.59.

I.R. (KBr) : 3420; 2970; 2540; 1640; 1430; 1120 $cm^{-1}$

Example 5

(R,S)-1-[(3S)-3-fluoropyrrolidin-1-yl]methyl-2-(4-trifluoromethyl phenyl)acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline.

Prepared as described in Example 2, starting from 1.3 g (4.96 mmoles) of (R,S)-1-[(3S)-3-fluoropyrrolidin-1-yl]methyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline, 1.43 g (6.42 mmoles) of distilled 4-trifluoromethylphenyl acetyl chloride and 0.69 g (4.96 mmoles) of anhydrous potassium carbonate in 25 ml of dry methylene chloride.
The crude product was purified by silica gel flash column chromatography, eluting with a mixture of EtOAc/n-hexane/28% $NH_4OH$, 25:25:0.2 respectively to yield 1.7 g of the pure free base which was recrystallized from n-hexane to yield 1.6 g of the title compound.

$C_{25}H_{28}F_4N_2O$

M.P. = 98-100°C
M.W. = 448.490

Elemental analysis: Calcd. C, 66.95; H, 6.29; N, 6.25; F, 16.95;
Found C, 66.87; H, 6.30; N, 6.22; F, 17.03.

I.R. (KBr) : 2980; 2800; 1630; 1610; 1450; 1410; 1330 $cm^{-1}$

Example 6

(R,S)-1-(4-trifluoromethylphenyl)acetyl-2-[(3S)-3-hydroxypyrrolidin-1-yl]methyl-4,4-dimethyl piperidine hydrochloride.

Prepared as described in Example 1, starting from 2.0 g (9.42 mmoles) of (RS)-2-[(3S)-3-fluropyrrolidin-1-yl]methyl-4,4-dimethyl piperidine and 2.09 g (9.39 mmoles) of distilled 4- trifluoromethyl phenyl acetyl chloride in 60 ml of dry DMF at a temperature of -15°C.
The crude product was purified by silica gel flash column chromatography, eluting with a mixture of $CH_2Cl_2$/MeOH/28% $NH_4OH$, 94.5:5:0.5 respectively to obtain 1.8 g of the pure free base

which was dissolved in ethyl acetate and the solution brought to acidic pH with $HCl/Et_2O$.
The precipitate was filtered, washed and dried to yield 1.6 g of the title compound.

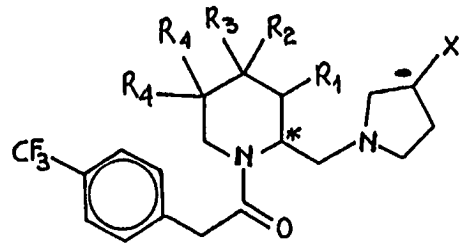
$C_{21}H_{29}F_3N_2O_2 \cdot HCl$

M.P. = 175-177°C
M.W. = 434.923

Elemental analysis: Calcd. C, 57.99; H, 6.95; N, 6.44;
Cl, 8.15, F, 13.11;
Found C, 57.89; H, 7.01; N, 6.39;
Cl, 8.18; f, 13.01.

I.R. (KBr) : 3240; 2940; 2620; 1630; 1440; 1130 $cm^{-1}$

TABLE I




| Example | * | ● | X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | MOLECULAR FORMULA | MELTING POINT (°C) | $[\alpha]_D^{20}$ (C=1,MeOH) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | R,S | R,S | OH | H | Me | Me | H | $C_{21}H_{29}F_3N_2O_2 \cdot HCl$ | 178-180 | - |
| 2 | S | S | F | H | H | H | H | $C_{19}H_{24}F_4N_2O \cdot HCl \cdot \frac{1}{2}H_2O$ | 151-153 | -45.3 |
| 3 | S | S | F | H | Me | Me | H | $C_{21}H_{28}F_4N_2O \cdot HCl$ | 156-157 | -33.8 |
| 4 | R,S | S | F | =CH-CH=CH-CH= | | | H | $C_{23}H_{24}F_4N_2O \cdot HCl$ | 195-197 | - |
| 5 | R,S | S | F | =CH-CH=CH-CH= | | | Me | $C_{25}H_{28}F_4N_2O$ | 98-100 | - |
| 6 | R,S | S | OH | H | Me | Me | H | $C_{21}H_{29}F_3N_2O_2 \cdot HCl$ | 175-177 | - |

The pharmacological activity of the compounds of this invention is illustrated by various in vitro and in vivo models, using the following test procedures, in which the mousetail flick test demonstrates analgesic activity.

PHARMACOLOGICAL TESTS

A) P-phenylquinone-induced abdominal writhing test in mice

The methodology employed is based on that described by Sigmund et al, Proc. Soc. Exptl. Biol. 95, 729/1957, modified by Milne and Twomey, Agents and Actions, 10, 31/1980.

Male Charles River mice (Swiss Strain), 25-36g body weight, were used. Animals were allowed food and water ad libitum and were randomized into groups of 10 prior to experimentation. Test compounds were dissolved in either distilled water or distilled water plus 0.1 M AMS, and administered by the subcutaneous route in a final volume of 10 ml/Kg. Control animals received 10 ml/Kg of the appropriate vehicle alone. Following a pretreatment period of 20 min., mice were injected intraperitoneally with p-phenylquinone, 2 mg/Kg at 37°C in a final volume of 10 mg/Kg. Next, the mice were placed, in groups of 3, in a compartmented perspex box maintained at room temperature and were observed for a period of 8 min. During this period the number of abdominal writhing responses per animal were recorded where writhing consists of an intermittent contraction of the abdomen associated with hind leg extension.

The degree of antinociceptive protection afforded by the test compound was determined as the mean number of writhing responses observed in the treated group (T) expressed as a percentage of the mean number of writhing responses in the

control group (C) according to the following formula:

[1-(T/C]x100% = % graded protection

B) Tail-flick test in mice

The methodology employed is based on that described by D'Amour and Smith, J. Pharmacol. Exp. Ther. 72, 74/1941.

Male Charles River mice (Swiss Strain), 22-34g body weight were used. Animals were allowed food and water ad libitum and were randomized into groups of 10 prior to experimentation. Before administration of the test compound, the reaction time of each animal was determined by focusing a beam of light onto the tail, eliciting a reflex withdrawal after a certain latency; only mice exhibiting a latency between 3-8 sec. were used subsequently in the evaluation of drug effects.

Test compounds were dissolved in either distilled water or distilled water plus 0.1 M AMS and administered by the subcutaneous route in a final volume of 10 ml/Kg. Control animals received 10 ml/kg of the appropriate vehicle alone. Following a pretreatment period of 30 min., the mice were again placed under the heat source and the reaction tine re-determined.

Percentage quantal protection was determined as the number of mice in which the reaction time was doubled compared to pretreatment values, expressed as a percentage of the total number of mice in the group.

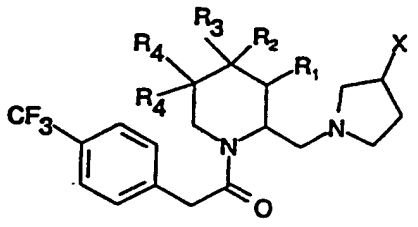
TABLE II

| EXAMPLE NO. | ANALGESIA | | DURATION OF ACTION M.TAIL-FLICK GRADED % ACTIVITY AT MTFQ ED50 | |
|---|---|---|---|---|
| | MOUSE WRITHING ED50 mg/kg sc | MOUSE TAIL-FLICK ED50 mg/kg sc | 30' | 90' |
| 1 | 0.088 | 1.113 | 82 | 98 |
| 2 | 0.0009 | 0.009 | 75 | 74 |
| 3 | 0.0016 | 0.012 | 85 | 54 |
| 4 | 0.00075 | 0.004 | 76 | 56 |
| 5 | 0.008 | 0.045 | 63 | 49 |
| 6 | 0.096 | 0.206 | 79 | 74 |

Data are referred to the free base.

Claims

1. A compound of formula (I), or a solvate or salt thereof,



(I)

in which each of $R_1$, $R_2$, $R_3$ and $R_4$ is hydrogen or methyl, and/or $R_1$, $R_2$ and $R_3$ together form a =CH-CH=CH-CH= group, and X is hydroxy or fluoro.

2. A compound according to claim 1, in which $R_1$ and $R_4$ are hydrogen, and $R_2$ and $R_3$ are methyl.

3. A compound according to claim 1, in which $R_1$, $R_2$, $R_3$ and $R_4$ are hydrogen.

4. 1-(4-trifluoromethylphenyl)acetyl-2-(3-hydroxypyrrolidin-1-yl)methyl-4,4-dimethyl piperidine.

5. (2S)-1-(4-trifluoromethylphenyl)acetyl-2-[(3S)-3-fluoropyrrolidin-1-yl)]methyl piperidine.

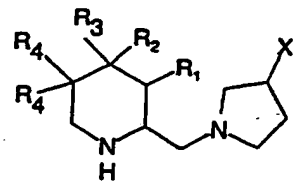
6. 1-(4-trifluoromethylphenyl)acetyl-2-[(3S)-3-fluoropyrrolidin-1-yl]methyl-4,4-dimethyl piperidine.

7. (R,S)-1-[(3S)-3-fluoropyrrolidin-1-yl]methyl-2-(4-trifluoromethylphenyl)acetyl-1,2,3,4-tetrahydroisoquinoline.

8. (R,S)-1-[(3S)-3-fluoropyrrolidin-1-yl]methyl-2-(4-trifluoromethylphenyl)acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline.

9. (R,S)-1-(4-trifluoromethylphenyl)acetyl-2-[(3S)-3-hydroxypyrrolidin-1-yl]methyl-4,4-dimethyl piperidine.

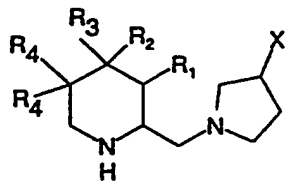
10. A process for the preparation of a compound of formula (I) according to any one of claims 1 to 9, which comprises reacting 4-trifluoromethylphenylacetic acid, or an active derivative thereof, with a compound of formula I(a)



(Ia)

in which $R_1$, $R_2$, $R_3$, $R_4$ and X are as defined in formula (I), and then optionally forming a salt and/or solvate of the obtained compound of formula (I).

11. A compound of formula I(a)



(Ia)

in which $R_1$, $R_2$, $R_3$, $R_4$ and X are as defined for formula (I) in claim 1.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

13. A compound according to any one of claims 1 to 9 for use as an active therapeutic substance.

14. A compound according to any one of claims 1 to 9 for use in the treatment of pain, convulsions, cough, asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states or cerebral ischaemia.

15. The use of a compound according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of pain, convulsions, cough, asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states or cerebral ischaemia.

16. A method for the treatment and/or prophylaxis of pain, convulsions, cough, asthma, inflammation, pancreatitis, arrhythmias, hyponatraemic disease states or cerebral ischaemia in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound according to any one of claims 1 to 9.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01111

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D211/26; C07D401/06

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07D |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| | WO,A,9 108 206 (ZAMBELETTI) 13 June 1991 cited in the application | |
| P,Y | see examples 5,23,25 | 1-16 |
| P,X | see claims 1-7,9-15 | 1-16 |
| | --- | |
| | EP,A,0 330 467 (GLAXO) 30 August 1989 cited in the application | |
| Y | see claims 1-4,6,9-11 | 1,3,5,7, 8,10-16 |
| X | * RN=125348-96-1 * | 11 |
| X | * RN= 125348-77-8 and 125348-78-9 * | 1,3, 12-16 |
| | --- | |
| | EP,A,0 330 469 (GLAXO) 30 August 1989 cited in the application | 1-16 |
| Y | see claims 1-5,7,9-13 | 1-16 |
| Y | see examples 7,8 | 1-16 |
| | --- | |
| | -/-- | |

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 08 JULY 1992 | 10. 08. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUR PEAN PATENT FFICE | BERND KASSLER |

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category* | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| A | EP,A,0 330 461 (GLAXO) 30 August 1989<br>cited in the application<br>see the whole document | 1-16 |
| P,Y | JOURNAL OF MEDICINAL CHEMISTRY.<br>vol. 35, no. 3, 7 February 1992, WASHINGTON US<br>pages 490 - 501;<br>SCOPES D. I. C ET. AL.: 'New kappa-receptor Agonists Based upon a 2-[(alkylamino)methyl]piperidine Nucleius'<br>see the whole document | 1-16 |
| Y | EP,A,0 361 791 (ZAMBELETTI) 4 April 1990<br>cited in the application<br>see examples 16,17 | 1-10,<br>12-16 |
| Y | see claims 1,3-12 | 1-16 |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9201111 SA 59970

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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| | | US-A- | 5089507 | 18-02-92 |